Functional neuromuscular junctions formed by embryonic stem cell-derived motor neurons.

Journal: PLoS One

Publication Year: 2012

Authors: Joy A Umbach, Katrina L Adams, Cameron B Gundersen, Bennett G Novitch

PubMed link: 22574134

Funding Grants: Molecular Characterization of hESC and hIPSC-Derived Spinal Motor Neurons

Public Summary:
A key objective of stem cell biology is to create physiologically relevant cells suitable for modeling disease pathologies in a cell culture setting. Much progress towards this goal has been made in the area of motor neuron disease through the development of methods to direct motor neuron formation from both embryonic and induced pluripotent stem cells, including those generated from disease patients. However, at present, there are few experimental systems available to assess motor neuron health and function. To address this challenge, we have developed a simplified culture system in which stem cell-derived motor neurons are grown together with muscle cells to facilitate the formation of functional neuromuscular connections. In this setting we were able to measure multiple parameters of motor neuron-muscle communication, and found that activity displayed by the stem cell-derived motor neurons accurately mirrors that seen with motor neurons and muscles in the body. This recording system thus provides a sensitive and quantitative analytical platform for evaluating the impact of motor neuron disease mutations on motor neuron-muscle communication.

Scientific Abstract:
A key objective of stem cell biology is to create physiologically relevant cells suitable for modeling disease pathologies in vitro. Much progress towards this goal has been made in the area of motor neuron (MN) disease through the development of methods to direct spinal MN formation from both embryonic and induced pluripotent stem cells. Previous studies have characterized these neurons with respect to their molecular and intrinsic functional properties. However, the synaptic activity of stem cell-derived MNs remains less well defined. In this study, we report the development of low-density co-culture conditions that encourage the formation of active neuromuscular synapses between stem cell-derived MNs and muscle cells in vitro. Fluorescence microscopy reveals the expression of numerous synaptic proteins at these contacts, while dual patch clamp recording detects both spontaneous and multi-quantal evoked synaptic responses similar to those observed in vivo. Together, these findings demonstrate that stem cell-derived MNs innervate muscle cells in a functionally relevant manner. This dual recording approach further offers a sensitive and quantitative assay platform to probe disorders of synaptic dysfunction associated with MN disease.